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ROUTING AND RECORD SHEET

SUBJECT: (Optional)

Federal Policy for Protection of Human Subjects

FROM:	EXTENSION	NO.
STAT Gary E. Foster Director of Medical Services 1 D 4061, Hdqs		ER 2982x/1 88 DATE 29 July 1988

TO: (Officer designation, room number, and building)	DATE RECEIVED	DATE FORWARDED	OFFICER'S INITIALS	COMMENTS (Number each comment to show from whom to whom. Draw a line across column after each comment.)
1. DDA	3 AUG 1988			OMS sees no problem with Agency concurrence in the Federal Policy for the Protection of Human Subjects. The proposed policy was developed by an Interagency Human Subjects Coordinating Committee which included an Agency representative from OMS. OMS recommends that the DCI sign the concurrence sheet (Enclosure E). This has been coordinated with [redacted] of the Administrative Law Division of OGC.
2. DDS&T	8 Aug			
3. ER	[illegible] 1988			
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ENCLOSURE A

5/26/88

____ CFR Part ____: Protection of Human Subjects

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§__.101 To What Does This Policy Apply?

(a) Except as provided in paragraph (b) of this section, this policy applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be

appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the federal government outside the United States.

(1) Research that is conducted or supported by a federal department or agency, whether or not it is regulated as defined in §___.102(e), must comply with all sections of this policy.

(2) Research that is neither conducted nor supported by a federal department or agency but is subject to regulation as defined in §___.102(e) must be reviewed and approved, in compliance with §___.101, §___.102, and §___.107 through §___.117 of this policy, by an institutional review board (IRB) that operates in accordance with the pertinent requirements of this policy.

(b) Unless otherwise required by department or agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

(1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

(i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability. or reputation.

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b) (2) of this section, if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

(4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

(5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs

or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(c) Department or agency heads retain final judgment as to whether a particular activity is covered by this policy.

(d) Department or agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the department or agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy.

(e) Compliance with this policy requires compliance with pertinent federal laws or regulations which provide additional protections for human subjects.

(f) This policy does not affect any state or local laws or regulations which may otherwise be applicable and which provide additional protections for human subjects.

(g) This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.

(h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly Declaration (Declaration of Helsinki amended 1983) issued either by sovereign states or by an organization whose function for the protection of human research subjects is internationally recognized.] In these circumstances, if a department or agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the FEDERAL REGISTER or will be otherwise published as provided in department or agency procedures.

(i) Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise covered by this policy. Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Protection from Research Risks, Department of

Health and Human Services (HHS), and shall also publish them in the FEDERAL REGISTER or in such other manner as provided in department or agency procedures.

§___.102 Definitions.

(a) "Department or agency head" means the head of any federal department or agency and any other officer or employee of any department or agency to whom authority has been delegated.

(b) "Institution" means any public or private entity or agency (including federal, state, and other agencies).

(c) "Legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(d) "Research" means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute "research" for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some "demonstration" and "service" programs may include research activities.

(e) "Research subject to regulation," and similar terms are intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity, (for example, Investigational New Drug requirements administered by the

Food and Drug Administration). It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).

(f) "Human subject" means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) data through intervention or interaction with the individual, or

(2) identifiable private information.

"Intervention" includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. "Interaction" includes communication or interpersonal contact between investigator and subject. "Private information" includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in

order for obtaining the information to constitute research involving human subjects.

(g) "IRB" means an institutional review board established in accord with and for the purposes expressed in this policy.

(h) "IRB approval" means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

(i) "Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(j) "Certification" means the official notification by the institution to the supporting department or agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

§___.103 Assuring Compliance with This Policy - Research Conducted or Supported by Any Federal Department or Agency.

(a) Each institution engaged in research which is covered by this policy and which is conducted or supported by a federal department or agency shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements set forth in this policy. In lieu of requiring

submission of an assurance, individual department or agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Protection from Research Risks, HHS, and approved for federalwide use by that office. When the existence of an HHS-approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to department and agency heads shall also be made to the Office for Protection from Research Risks, HHS.

(b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. Assurances applicable to federally supported or conducted research shall at a minimum include:

(1) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to federal regulation. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the institution itself. This requirement does not preempt

provisions of this policy applicable to department- or agency-supported or regulated research and need not be applicable to any research exempted or waived under §___.101(b) or (i).

(2) Designation of one or more IRBs established in accordance with the requirements of this policy, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

(3) A list of the IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant. Changes in IRB membership shall be reported to the department or agency head. unless in accord with §___.103(a) of this policy, the existence of an HHS-approved assurance is accepted. In this case, change in IRB membership shall be reported to the Office for Protection from Research Risks, HHS.

(4) Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and

(iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(5) Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head (i) any unanticipated problems or scientific misconduct involving risks to human subjects or others; (ii) any instance of serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval.

(c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this policy and shall be filed in such form and manner as the department or agency head prescribes.

(d) The department or agency head will evaluate all assurances submitted in accordance with this policy through such officers and employees of the department or agency and such experts or consultants engaged for this purpose as the department or agency head determines to be appropriate. The department or agency head's evaluation will take into consideration the adequacy of the proposed IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of

the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

(e) On the basis of this evaluation, the department or agency head may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The department or agency head may limit the period during which any particular approved assurance or class of approved assurances shall remain effective or otherwise condition or restrict approval.

(f) Certification is required when the research is supported by a federal department or agency and not otherwise exempted or waived under §___.101(b) or (i). An institution with an approved assurance shall certify that each application or proposal for research covered by the assurance and by §___.103 of this Policy has been reviewed and approved by the IRB. Such certification must be submitted with the application or proposal or by such later date as may be prescribed by the department or agency to which the application or proposal is submitted. Under no condition shall research covered by §___.103 of the Policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research shall certify within 30 days after receipt of a request for such a certification from the department or agency, that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

§__.104 [Reserved]

§__.105 [Reserved]

§__.106 [Reserved]

§__.107 IRB Membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons

of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

§___.108 IRB Functions and Operations.

In order to fulfill the requirements of this policy each IRB shall:

(a) Follow written procedures in the same detail as described in §___.103(b)(4) and, to the extent required by, §___.103(b)(5).

(b) Except when an expedited review procedure is used (see §___.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific

areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

§___.109 IRB Review of Research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with Sec.116. The IRB may require that information, in addition to that specifically mentioned in §___.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with §___.117.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have

authority to observe or have a third party observe the consent process and the research.

§ ___.110 Expedited Review Procedures for Certain Kinds of Research Involving No More than Minimal Risk, and for Minor Changes in Approved Research.

(a) The Secretary, HHS, has established, and published as a Notice in the FEDERAL REGISTER, a list of categories of research that may be reviewed by the IRB through an expedited review procedure.1/ The list will be amended, as appropriate after consultation with other departments and agencies, through periodic republication by the Secretary, HHS, in the FEDERAL REGISTER. A copy of the list is available from the Office for Protection from Research Risks, National Institutes of Health, HHS, Bethesda, Maryland 20892.

(b) With the approval of department or agency heads, an IRB may use the expedited review procedure to review either or both of the following:

(1) some or all of the research appearing on the list and found by the reviewers to involve no more than minimal risk,

(2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the

1/ See elsewhere in the Part of this issue of the FEDERAL REGISTER.

reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in §___.108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

§___.111 Criteria for IRB Approval of Research.

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible

long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §___.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §___.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional

safeguards have been included in the study to protect the rights and welfare of these subjects.

§___.112 Review by Institution.

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§___.113 Suspension or Termination of IRB Approval of Research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.

§___.114 Cooperative Research.

Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB,

or make similar arrangements for avoiding duplication of effort.

§___.115 IRB Records.

(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members in the same detail as described in §___.103(b)(3).

(6) Written procedures for the IRB in the same detail as described in §___.103(b)(4) and §___.103(b)(5).

(7) Statements of significant new findings provided to subjects, as required by §___.116(b)(5).

(b) The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner.

§___.116 General Requirements for Informed Consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

(6) The approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

(2) The research could not practicably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research involves no more than minimal risk to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) The research could not practicably be carried out without the waiver or alteration; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

(e) The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

§___.117 Documentation of Informed Consent.

(a) Except as provided in paragraph (c) of this section, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

(b) Except as provided in paragraph (c) of this section, the consent form may be either of the following:

(1) A written consent document that embodies the elements of informed consent required by §___.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed; or

(2) A "short form" written consent document stating that the elements of informed consent required by §___.116 have been presented orally to the subject or the subject's legally

authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative, in addition to a copy of the "short form."

(c) An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

(1) That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

(2) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

§___.118 Applications and Proposals Lacking Definite Plans for Involvement of Human Subjects.

Certain types of applications for grants, cooperative agreements, or contracts are submitted to departments or agencies with the knowledge that subjects may be involved within the period of support, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These applications need not be reviewed by an IRB before an award may be made. However, except for research exempted or waived under §___.101(b) or (i), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in this policy, and certification submitted, by the institution, to the department or agency.

§___.119 Research Undertaken Without the Intention of Involving Human Subjects.

In the event research is undertaken without the intention of involving human subjects, but it is later proposed to involve human subjects in the research, the research shall first be reviewed and approved by an IRB, as provided in this policy, a certification submitted, by the institution, to the

department or agency, and final approval given to the proposed change by the department or agency.

§___.120 Evaluation and Disposition of Applications and Proposals for Research to be Conducted or Supported by a Federal Department or Agency.

(a) The department or agency head will evaluate all applications and proposals involving human subjects submitted to the department or agency through such officers and employees of the department or agency and such experts and consultants as the department or agency head determines to be appropriate. This evaluation will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained.

(b) On the basis of this evaluation, the department or agency head may approve or disapprove the application or proposal, or enter into negotiations to develop an approvable one.

§___.121 [Reserved]

§___.122 Use of Federal Funds.

Federal funds administered by a department or agency may not be expended for research involving human subjects unless the requirements of this policy have been satisfied.

§___.123 Early Termination of Research Support; Evaluation of Applications and Proposals.

(a) The department or agency head may require that department or agency support for any project be terminated or suspended in the manner prescribed in applicable program requirements, when the department or agency head finds an institution has materially failed to comply with the terms of this policy.

(b) In making decisions about supporting or approving applications or proposals covered by this policy the department or agency head may take into account, in addition to all other eligibility requirements and program criteria, factors such as whether the applicant has been subject to a termination or suspension under paragraph (a) of this section and whether the applicant or the person or persons who would direct or has have directed the scientific and technical aspects of an activity has have, in the judgment of the department or agency head, materially failed to discharge responsibility for the protection of the rights and welfare of human subjects (whether or not the research was subject to federal regulation).

§___.124 Conditions.

With respect to any research project or any class of research projects the department or agency head may impose additional conditions prior to or at the time of approval when in the judgment of the department or agency head additional conditions are necessary for the protection of human subjects.

ENCLOSURE B

7/1/88

INTERAGENCY HUMAN SUBJECTS COORDINATING COMMITTEE

List of Department and Agency Contacts

of the

Federal Coordinating Council for Science,

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DEPARTMENT OF EDUCATION

34 CFR Part 97

1. It is proposed that Title 34 of the Code of Federal Regulations be amended by adding Part 97 as set forth at the end of this document.

PART 97 PROTECTION OF HUMAN SUBJECTS

Sec.

Authority: 5 U.S.C. 301; 42 U.S.C. 300v-1(b); §97.101(b)(3) issued under 20 U.S.C. 1221-3(a)(1), 3474.

2. Part 97 is further amended by revising paragraph (b)(3) of §97.101 to read as follows:

§97.101 To What Does This Policy Apply?

* * * * *

(b) * * *

(3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement) survey procedures, interview procedures or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) the research is conducted under a program subject to the protections of the General Education Provisions Act (GEPA), including GEPA Sections 400A (20 U.S.C. 1221-3), 438 (20 U.S.C. 1232g), and 439 (20 U.S.C. 1232h).

* * * * *

3. Part 97 is further amended by revising paragraph (a) of §97.107 to read as follows:

§97.107 IRB Membership

(a) - Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to

ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. When an IRB reviews research that deals with the handicapped children or mentally disabled persons, the IRB shall include at least one person primarily concerned with the welfare of the research subjects. If an IRB regularly reviews another vulnerable category of subjects, such as non-handicapped children, prisoners, or pregnant women, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

* * * * *

Signature: _____

Name of Signer: _____

Title: _____

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

21 CFR PARTS 50 AND 56

[DOCKET NO. 87N-0032]

PROTECTION OF HUMAN SUBJECTS; INFORMED CONSENT; STANDARDS FOR INSTITUTIONAL REVIEW BOARDS FOR CLINICAL INVESTIGATIONS

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend (1) its regulations that contain the general standards for any institutional review board (IRB) that reviews clinical investigations regulated by the agency and (2) its regulations that establish general requirements for informed consent of human subjects that participate in such research. The agency intends to conform its regulations to the extent possible to the "~~Model~~ Federal Policy for the Protection of Human ~~Research~~ Subjects" (Model Policy) published elsewhere in this issue of the FEDERAL REGISTER. Existing FDA regulations governing protection of human subjects share a common core with the Model Policy and implement the fundamental principles embodied in that policy. The purpose of these proposed amendments is to eliminate certain inconsistencies with the Model Policy.

5/10/88

87-50

DATE: Comments by (insert date 60 days after date of publication in the FEDERAL REGISTER).

ADDRESS: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

BACKGROUND

Development of Model Policy

FDA is charged by statute with the obligation of ensuring the protection of the rights, safety, and welfare of human subjects who participate in clinical investigations involving articles subject to section 505(i), 507(d), or 520(g) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(i), 357(d), or 360j(g)), as well as clinical investigations that support applications for research or marketing permits for products regulated by FDA, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. In performance of that obligation,

FDA, in the FEDERAL REGISTER of January 27, 1981, adopted regulations governing informed consent of human subjects (21 CFR Part 50; 46 FR 8942) and regulations establishing standards for the composition, operation, and responsibilities of any IRB that reviews clinical investigations involving human subjects (21 CFR Part 56; 46 FR 8958). At the same time, the Department of Health and Human Services (HHS) also adopted regulations on the protection of human research subjects (45 CFR Part 46). The regulations adopted by FDA in 21 CFR Parts 50 and 56 and by HHS in 45 CFR Part 46 have provided a common framework for clinical investigators, any IRB, and institutions that have been involved in research that is subject to FDA's regulatory requirements or that is funded by HHS.

In December 1981, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research issued its "First Biennial Report on the Adequacy and Uniformity of Federal Rules and Policies, and Their Implementation, for the Protection of Human Subjects in Biomedical and Behavioral Research, Protecting Human Subjects." Included in this report was a recommendation that the regulations issued by HHS (45 CFR Part 46) be adopted as a common core by all Federal departments and agencies, while permitting additions needed by any department or agency that were not inconsistent with these core provisions.

In May 1982, The President's Science Advisor, Office of Science and Technology Policy (OSTP), appointed an Ad Hoc Committee for the Protection of Human Research Subjects, under the auspices of the Federal Coordinating Council for Science, Engineering, and Technology (FCCSET), to respond to the recommendations of the President's Commission. The Committee was composed of representatives and ex-officio members from departments and agencies that conduct, support, or regulate research involving human subjects. The Ad Hoc Committee developed responses to the recommendations of the President's Commission in consultation with OSTP and the Office of Management and Budget (OMB).

The Ad Hoc Committee agreed that uniformity of Federal regulations is desirable to eliminate unnecessary regulations and to promote increased understanding by institutions that conduct federally supported or regulated research involving human subjects. The Ad Hoc Committee developed a model policy which OSTP later modified and, with the concurrence of all affected Federal departments and agencies, published as a proposal in the FEDERAL REGISTER of June 3, 1986 (51 FR 20204). More than 200 written comments were submitted in response to the proposal. These comments were considered by the Interagency Human Subjects Coordinating Committee, a second committee chartered by FCCSET in 1983. This committee is composed of representatives of all Federal departments and agencies that conduct, support, or regulate research involving human subjects. Published elsewhere in this issue of the FEDERAL REGISTER is the final Model Policy.

FDA concurs with the final Model Policy. However, FDA must diverge from sec. 101(h) of the final Model Policy with regard to those clinical investigations that take place in a foreign country and are conducted under a research permit granted by FDA. Such investigations must be carried out in accordance with the act, which establishes certain requirements for the conduct of such investigations (see, e.g., 21 U.S.C. 355(i), 357(d)(3), and 360j(g)). For these investigations, FDA does not have the authority to accept the procedures followed in a foreign country in lieu of the procedures required by the act. FDA must also depart from sec. 116(d) of the final Model Policy (see 21 CFR 50.20). The act requires that informed consent be obtained from all subjects of clinical investigations except in very limited circumstances (see, e.g., 21 U.S.C. 355(i), 357(d)(3), and 360j(g)(3)(D), which establish requirements for the conduct of clinical investigations for drugs, antibiotic drugs, and medical devices, respectively). FDA does not have the authority under the act to waive this requirement.

Accordingly, the agency is committed to being as consistent with the final Model Policy as it can be, given the unique situation created by the act and the fact that FDA only regulates, and does not support or conduct, research under its regulations. For all these reasons, the agency proposes the following amendments to its regulations in Parts 50 and 56 to conform them to the final Model Policy to the extent permitted by the act. The proposed changes

are minor, and FDA believes that they would not require significant modifications in current IRB procedures or operations or in how informed consent is obtained from human subjects who participate in clinical investigations.

PROPOSED REVISIONS OF FDA'S REGULATIONS

Definitions

1. FDA proposes to revise the definition of "minimal risk" in §§ 50.3(l) and 56.102(i) to conform it to the definition in the Model Policy. The current definition in §§ 50.3(l) and 56.102(i) of FDA's regulations states:

> "Minimal risk" means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

The wording of the definition of "minimal risk" in sec. 102(i) of the final Model Policy is slightly different. To make its regulations as consistent as possible with the Model Policy, FDA is proposing to adopt that policy's definition of "minimal risk." Accordingly, FDA is proposing to revise §§ 50.3(l) and 56.102(i) to state:

> "Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

FDA believes that the proposed change in wording does not substantively change the current definition of "minimal risk" as it pertains to research regulated by the agency. Rather, it clarifies FDA's current definition.

2. FDA proposes to add to the IRB regulations a definition of "IRB approval," which is included in sec. 102(h) of the final Model Policy. The definition of "IRB approval" in proposed new § 56.102(m) is provided to conform

FDA's regulations with the Model Policy and for clarification. It is consistent with the agency's policy respecting IRB approval under current Part 56.

Exemptions from IRB Requirement

3. In new § 56.104(d), FDA proposes to add to the list of categories of clinical investigations that are exempt from the requirements for IRB review certain taste and food quality evaluation studies. This exemption is provided in the final Model Policy at sec. 101(b)(6), in response to a request from the U.S. Department of Agriculture (USDA), but it is also appropriate for FDA. The exemption would apply only to taste tests and quality evaluation studies of foods that are not adulterated and that contain ingredients that are (1) generally recognized as safe (GRAS) (see 21 CFR Parts 170, 182, 184, and 186), (2) used in accordance with FDA's food additive regulations, or (3) used in accordance with an approval issued by USDA or the Environmental Protection Agency.

IRB Membership

4. FDA is proposing to amend § 56.107(a) in several respects to conform it to the language contained in sec. 107(a) of the final Model Policy. First, instead of the current provision in FDA's regulations that specifies that

an IRB shall be sufficiently qualified through, among other factors, "* * * the diversity of the members' backgrounds including consideration of the racial and cultural backgrounds of members * * *," the agency proposes to substitute "* * * the diversity of the members, including consideration of race, gender, and cultural backgrounds * * *."

This proposed change would add gender to the considerations of diversity. The addition of gender emphasizes the importance of including both men and women as members of any IRB. FDA considers this change to be necessary in light of the change that it is proposing to make in § 56.107(b), which is discussed in paragraph 5 of this preamble.

In addition, to conform to the language contained in sec. 107(a) of the final Model Policy, FDA is proposing to modify the requirement in § 56.107(a) that an IRB that regularly reviews research that involves a vulnerable category of subjects include one or more individuals who are primarily concerned with the welfare of those subjects. FDA is proposing to require only that the institution (or other authority) that establishes the IRB consider including such an individual as a member of such an IRB. FDA expects that, even if it makes this change in its regulations, institutions will continue to appoint individuals to the IRB who are primarily concerned with the welfare of vulnerable subject populations in appropriate situations.

Finally, FDA proposes to add the following examples of vulnerable populations to § 56.107(a): children, prisoners, pregnant women, or mentally disabled persons. FDA is proposing this change in the regulation to conform it to the final Model Policy and to make clear the types of human subjects that the agency considers to be "vulnerable populations."

5. In current § 56.107(b), FDA provides that an IRB may not consist entirely of men or entirely of women, or entirely of members of one profession. FDA proposes to revise § 56.107(b) to require that:

> Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

This language was developed by OSTP in consultation with the U.S. Department of Justice and is included in sec. 107(b) of the final Model Policy to make clear that an individual should not be appointed to an IRB solely because of gender. FDA proposes to revise § 56.107(b) accordingly.

As provided in § 56.107(a), however, in seeking diverse membership on the IRB, the institution must consider both men and women who can contribute to the work of the IRB. Given the ready availability of well-qualified persons of both genders, FDA expects that only rarely, if ever, will an IRB consist solely of men or solely of women.

6. FDA proposes to revise § 56.107(c), which currently requires each IRB to include at least one member whose primary concerns are in nonscientific areas, to conform to the language contained in final sec. 107(c) of the Model Policy. As revised, § 56.107(c) would require that each IRB include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas. These changes should not affect any IRB that reviews research regulated by FDA. As described in the preamble to the 1981 IRB regulations (46 FR 8966), FDA's current regulations assume that an IRB will include at least one qualified scientist:

> * * * FDA emphasizes that § 56.107(a) requires that IRBs have as members persons with the professional competence necessary to review the proposed research. For example, FDA would expect that an IRB that reviews investigational new drug studies will include at least one physician.

FDA expects that institutions will continue to use good judgment and diligence in selecting as IRB members persons who can fulfill the requirements of § 56.107(a), so that persons of varying backgrounds will be included on any IRB to ensure complete and adequate review of the research activities.

Should FDA adopt the proposed amendment, in inspecting any IRB, the agency will continue to review an IRB's composition to ensure that its membership is appropriate for the research it is charged to review and may request that membership be supplemented if complete and adequate review of the research does not appear possible.

IRB Functions and Operations

To be consistent with the language contained in sec. 103(b)(4) and (5) of the final Model Policy, FDA is proposing to remove § 56.108(a)(5) and (c), redesignate current § 56.108(b) as § 56.108(c), and add new § 56.108(b) that would state:

> Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of (1) any

unanticipated problems or scientific misconduct involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; and (3) any suspension or termination of IRB approval.

New § 56.108(b) would incorporate the requirements currently included in § 56.108(a)(5) and (c) of FDA's regulations, conform them to the final Model Policy, and respond to recommendations 7 and 8 of the President's Commission concerning scientific misconduct in research involving human subjects, as described in the preamble to the proposed Model Policy (51 FR 20209, 20210). New § 56.108(b) would effect three changes in FDA's regulations.

a. The major change is to require prompt reporting of scientific misconduct involving risks to human subjects or others while allowing institutions the flexibility to develop their own procedures. These procedures must assure that instances of scientific misconduct are promptly reported to the IRB, to appropriate institutional officials, and to FDA. Institutions will, therefore, be afforded flexibility in meeting the requirements of the regulations.

b. The current regulations require that an IRB follow written procedures that ensure prompt reporting to the IRB of unanticipated problems involving risks to subjects or others. Proposed § 56.108(b) would require that an IRB follow written procedures that ensure prompt reporting of unanticipated problems not only to the IRB but also to appropriate institutional officials and FDA.

c. Finally, FDA's current regulations provide that the IRB is responsible for reporting any instance of serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB, and any suspension or termination of IRB approval, to appropriate institutional officials and to FDA. FDA is proposing to require that these responsibilities be reflected in the written procedures of the IRB.

These proposed changes would ensure that the IRB, the institution, and FDA are informed of problems and misconduct based on noncompliance with the regulations. Because of the importance that FDA attaches to ensuring that the IRB, the institution, and FDA are so informed, the agency has tentatively determined that the obligation to notify these bodies should be reflected in the IRB's written procedures.

Expedited Review Procedures
for Certain Kinds of Research Involving
No More Than Minimal Risk and for
Minor Changes in Approved Research

8. FDA proposes to revise § 56.110(b) to conform it to the language contained in sec. 110(b) of the final Model Policy. The first and second sentences of § 56.110(b) currently provide that:

> An IRB may review some or all of the research appearing on [a list published in the FEDERAL REGISTER of January 27, 1981; 46 FR 8980] through an expedited review procedure, if the research involves no more than minimal risk. The IRB may also use the expedited review procedure to review minor changes in previously approved research during the period for which approval is authorized.

FDA proposes to revise this language to s ce:

> An IRB may use the expedited review procedure to review either or both of the following: (1) some or all of the research appearing on the list and found by the reviewers to involve no more than minimal risk, (2) minor changes in previously approved research during the period (of 1 year or less) for which approval is authorized.

FDA believes that this change would not in any way change the substance of the regulation or the circumstances in which expedited review may be used.

Criteria for IRB Approval of Research

9. FDA proposes to revise § 56.111(a)(3) and (b) to conform its regulations to the language contained in sec. 111(a)(3) and (b) of the final Model Policy. As discussed below, these proposed revisions would both clarify and reinforce current regulatory requirements.

FDA would retain the current wording in § 56.111(a)(3), but at the end of the provision would add the phrase "and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons."

This proposed addition would conform § 56.111(a)(3) to the language contained in sec. 111(a)(3) of the final Model Policy and would reinforce the protections in § 56.107 for vulnerable populations.

FDA is proposing three changes in § 56.111(b) to conform it to the language contained in the Model Policy. The first proposed change would delete the phrase "such as persons with acute or severe physical or mental illness" from the examples given of subjects likely to be vulnerable to coercion or undue influence. Although this category of subjects would no longer be explicitly included in § 56.111(b), FDA would continue to regard these persons as being likely to be vulnerable to coercion or undue influence and would expect an IRB to ensure that appropriate additional safeguards have been included in a study to protect the rights and welfare of such subjects. The second proposed change would clarify which groups of subjects are likely to be vulnerable to coercion or undue influence, by giving examples from sec. 111(b) of the final Model Policy.

The groups mentioned are children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons. The third change that the agency is proposing is to delete the word "appropriate" from the requirement that, where necessary "* * * additional safeguards have been included in the study to protect the rights and welfare of these subjects." FDA expects that any additional safeguards that are recommended in a study would be appropriate to protect the rights and welfare of subjects included in the study, and, therefore, inclusion of the word "appropriate" is unnecessary.

IRB Records

10. FDA is proposing to revise § 56.115(a)(6) to cross-reference proposed § 56.108(b), which would require the IRB to follow written procedures for certain reporting requirements. The agency proposes this change for consistency with the Model Policy and, therefore, considers it to be minor.

ENVIRONMENTAL IMPACT

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

PAPERWORK REDUCTION ACT OF 1980

Sections 56.108(b) and 56.115 of this proposed rule contain collection of information requirements subject to approval by the Office of Management and Budget under the terms of the Paperwork Reduction Act. Comments on these requirements should be submitted to FDA's Dockets Management Branch (address above) and to Mr. Richard Eisinger, Office of Management and Budget, Executive Office of the President, Room 3002, New Executive Office Building, Washington, DC 20503.

ECONOMIC AND REGULATORY ASSESSMENTS

FDA has examined the economic consequences of the proposed amendments to its regulations pertaining to any IRB and to informed consent in accordance with the criteria in section 1(b) of Executive Order 12291 and found that these amendments, if promulgated, would not be a major rule under the Executive Order. The agency also has considered the effect that the proposed rule would have on small entities including small businesses in accordance with the Regulatory Flexibility Act (Pub. L. 96-354). The agency certifies that there will not be a significant economic impact on a substantial number of small entities.

The proposed amendments are intended to bring FDA's regulations on informed consent of human subjects that participate in clinical research (21 CFR Part 50) and on general standards for any IRB that reviews clinical investigations regulated by the agency (21 CFR Part 56) into conformance with the Model Policy to the extent possible. The proposed amendments have three kinds of impact.

First, there are nomenclature, definitional, and clarifying changes that do not alter the current usage or meaning of the terms in the regulations. These changes have no impact on IRB functions or operations.

Second, there are two changes that clearly benefit an IRB and the research community in general. One exempts certain taste and food quality evaluation studies from IRB review. The other allows for greater flexibility in determining the composition of any IRB.

Third, there is the change, responding to recommendations in the preamble to the Model Policy, which necessitates adding "unanticipated problems or scientific misconduct" to a list of items that are to be reported to the IRB, the institution, and to the agency, and requires the IRB to adopt and follow written procedures for two responsibilities held under the current regulations. Incorporating these requirements into existing IRB written procedures should require at most a paragraph. The agency does not consider this to be a material burden on any IRB, regardless of size.

Thus, these proposed amendments are considered to have no significant effect, either positive or negative, on the institutions overseeing clinical research.

REQUEST FOR COMMENTS

Interested persons may, on or before (insert date 60 days after date of publication in the FEDERAL REGISTER), submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the

docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR

Part 50: Prisoners, Reporting and recordkeeping requirements, Research, Safety.

Part 56: Reporting and recordkeeping requirements, Research, Safety.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, it is proposed that Parts 50 and 56 be amended as follows:

PART 50--PROTECTION OF HUMAN SUBJECTS

1. The authority citation for 21 CFR Part 50 is revised to read as follows:

AUTHORITY: Secs. 201, 406, 409, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 701(a), 706, and 801, Pub. L. 717, 52 Stat. 1040-1042 as amended, 1049-1054 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463 as amended, 72 Stat. 1785-1788 as amended, 74 Stat. 399-407 as amended, 76 Stat. 794-795 as amended, 90 Stat. 540-560, 562-574 (21 U.S.C. 321, 346, 348, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 371(a), 376, and 381); secs. 215, 351, 354-360F, Pub. L. 410, 58 Stat. 690, 702 as amended, 82 Stat. 1173-1186 as amended (42 U.S.C. 216, 262, 263b-263n); 21 CFR 5.10.

2. In § 50.3 by revising paragraph (l) to read as follows:

§ 50.3 Definitions.

* * * * *

(l) "Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

* * * * *

PART 56--INSTITUTIONAL REVIEW BOARDS

3. The authority citation for 21 CFR Part 56 is revised to read as follows:

AUTHORITY: Secs. 201, 406, 408, 409, 501, 502, 503, 505, 506, 507, 510, 513-516, 518-520, 701(a), 706, and 801, Pub. L. 717, 52 Stat. 1040-1042 as amended, 1049-1054 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463 as amended, 68 Stat. 511-518 as amended, 72 Stat. 1785-1788 as amended, 74 Stat. 399-407 as amended, 76 Stat. 794-795 as amended, 90 Stat. 540-546, 560, 562-574 (21 U.S.C. 321, 346, 346a, 348, 351, 352, 353, 355, 356, 357, 360, 360c-360f, 360h-360j, 371(a), 376, and 381), secs. 215, 301, 351, 354-360F, Pub. L. 410, 58 Stat. 690, 702 as amended, 82 Stat. 1173-1186 as amended (42 U.S.C. 216, 241, 262, 263b-263n); 21 CFR 5.10.

4. In § 56.102 by revising paragraph (i) and adding new paragraph (m) to read as follows:

§ 56.102 Definitions.

* * * * *

(i) "Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

* * * * *

(m) "IRB approval" means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.

5. In § 56.104 by adding paragraph (d) to read as follows:

§ 56.104 Exemptions from IRB requirement.

* * * * *

(d) Taste and food quality evaluation and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

6. In § 56.107 by revising paragraphs (a), (b), and (c) to read as follows:

§ 56.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

(b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

* * * * *

7. In § 56.108 by removing paragraph (c), redesignating paragraph (b) as paragraph (c), revising paragraph (a), and adding paragraph (b) to read as follows:

§ 56.108 IRB functions and operations.

* * * * *

(a) Follow written procedures (1) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (2) for determining which projects require

review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; (3) for ensuring prompt reporting to the IRB of changes in a research activity; and (4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

(b) Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of (1) any unanticipated problems or scientific misconduct involving risks to human subjects or others; (2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; and (3) any suspension or termination of IRB approval.

* * * * *

8. In § 56.110 by revising paragraph (b) to read as follows:

§ 56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk and for minor changes in approved research.

* * * * *

(b) An IRB may use the expedited review procedure to review either or both of the following: (1) some or all of the research appearing on the list and found by the reviewers to involve no more than minimal risk, (2) minor changes in previously approved research during the period (of 1 year or less) for which approval is authorized. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the nonexpedited procedure set forth in § 56.108(c).

* * * * *

9. In § 56.111 by revising paragraphs (a)(3) and (b) to read as follows:

§ 56.111 Criteria for IRB approval of research.

(a) * * *

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

* * * * *

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

10. In § 56.115 by revising paragraph (a)(6) to read as follows:

§ 56.115 IRB records.

(a) * * *

(6) Written procedures for the IRB as required by § 56.108(a) and (b).

* * * * *

John A. Norris
Acting Commissioner of Food and Drugs

Otis R. Bowen
Secretary of Health and Human Services

Dated: _____.

FEDERAL POLICY FOR THE PROTECTION OF HUMAN SUBJECTS

AGENCIES:

United States Department of Agriculture
Department of Energy
National Aeronautics and Space Administration
Department of Commerce
Consumer Product Safety Commission
Agency for International Development
Department of Housing and Urban Development
Department of Justice
Department of Defense
Department of Education
Veterans Administration
Environmental Protection Agency
National Science Foundation
Department of Health and Human Services
Department of Transportation

ACTION: Notice of Proposed Rulemaking

SUMMARY: This document sets forth a common Federal Policy for the Protection of Human Subjects accepted by the Office of Science Technology Policy and proposes the adoption of that Policy in regulation by each of the listed Departments and Agencies. A Proposed Model Federal Policy published in June 1986 (51 FR 20204) was revised in response to public comments. The Policy as revised is now set forth as a common Notice of Proposed Rulemaking. Additional public comments are solicited concerning adoption of the Policy by each of the listed Departments and Agencies and the proposed departures from the Policy described herein. For related documents, see other sections of this Part of this Federal Register issue.

DATES: To be assured of consideration, comments must be in writing and must be received on or before 5:00 p.m. on [60 days from date of publication].

ADDRESSES: Please send comments or requests for additional information to: Dr. Joan P. Porter, Office for Protection from Research Risks, National Institutes of Health, Building 31, Room 4B09, Bethesda, MD 20892. Comments directed toward adoption of the common Federal Policy by a particular Department or Agency should be clearly identify that Department or Agency.

Comments should refer to specific sections in the proposed regulations. Comments received will be available for public inspection at the National Institutes of Health, Building 31, Room 4B09, Bethesda, Maryland, from 9:00 a.m. to 4:00 p.m. Monday through Friday except legal holidays.

PAPERWORK REDUCTION ACT REQUIREMENTS: Sections _____.103(b); _____.109(d); _____.113; _____.115; _____.116; and _____.117 contain information collection requirements subject to approval by the Office of Management and Budget under the terms of the Paperwork Reduction Act. Comments on these requirements should be submitted to Dr. Joan Porter at the address noted and to Mr. Richard Eisinger, Office of Management and Budget, Executive Office of the President, Room 3002, New Executive Office Building, Washington, D.C. 20503.

FOR FURTHER INFORMATION CONTACT: Dr. Joan P. Porter, (301) 496-7005.

SUPPLEMENTARY INFORMATION:

Background

The purpose of the common Notice of Proposed Rulemaking is to request public comment on implementation of a common Federal Policy for the protection of human subjects of research conducted, supported or regulated by the following Federal Departments and Agencies: United States Department of Agriculture, Department of Energy, National Aeronautics and Space Administration, Department of Commerce, Consumer Product Safety Commission, Agency for International Development, Department of Housing and Urban Development, Department of Justice, Department of Defense, Department of Education, Veterans Administration, Environmental Protection Agency, National Science Foundation, Department of Health and Human Services, Department of Transportation. Each of these Departments and Agencies would adopt the common rule in total except as indicated in the departures for the Department of Education published herein, as regulations to be codified as listed above.

The Food and Drug Administration (FDA) Notice of Proposed Rulemaking to modify current regulations to conform to the Federal Policy is presented elsewhere in this Part. Public comment is requested concerning the FDA Notice of Proposed Rulemaking. Comment regarding the Department of Education departures is also solicited.

Adoption of the common Federal Policy by these Departments and Agencies will implement a recommendation of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research which was established on November 9, 1978, by P.L. 95-622. One of the charges to the President's Commission was to report biennially to the President, the Congress, and appropriate Federal Departments and Agencies on the protection of human subjects of biomedical and behavioral research. In carrying out that charge, the President's Commission was directed to conduct a review of the adequacy and uniformity (1) of the rules, policies, guidelines, and regulations of all Dederal Departments and Agencies regarding the protection of human subjects of biomedical or behavioral research which such departments and agencies conduct or support, and (2) of the implementation of such rules, policies, guidelines, and regulations by such agencies, such review to include appropriate recommendations for legislation and administrative action.

In December 1981 the President's Commission issued its First Biennial Report on the Adequacy and Uniformity of Federal Rules and Policies, and their Implementation, for the Protection of Human Subjects in Biomedical and Behavioral Research, Protecting Human Subjects.

In accord with P.L. 95-622, each Federal Department or Agency which receives recommendations from the President's Commission with respect to its rules,

policies, guidelines or regulations, must publish the recommendations in the Federal Register and provide an opportunity for interested persons to submit written data, views and arguments with respect to adoption of the recommendations. On March 29, 1982 (47 FR 13272-13305), the Secretary, HHS published the recommendation on behalf of the affected Departments and Agencies.

In May 1982 the Chairman of the Federal Coordinating Council for Science, Engineering, and Technology (FCCSET), appointed an Ad Hoc Committee for the Protection of Human Research Subjects under the auspices of the FCCSET. The Committee, chaired by Dr. Edward N. Brandt, Jr., Assistant Secretary for Health, Department of Health and Human Services (HHS), was composed of the representatives and ex-officio members of affected Departments and Agencies. In consultation with the Office of Science and Technology Policy (OSTP) and the Office of Management and Budget, the Ad Hoc Committee, after considering all public comments, developed responses to the recommendations of the President's Commission. After further review and refinement, OSTP responded on behalf of all the affected Department and Agency heads to the recommendations of the President's Commission, including the recommendation that:

> The President should, through appropriate action, require that all federal departments and agencies adopt as a common core the regulations governing research with human subjects issued by the Department of Health and Human Services (codified at 45 CFR 46), as periodically amended or revised, while permitting additions needed by any department or agency that are not inconsistent with these core provisions.

The Ad Hoc Committee agreed that uniformity is desirable among Departments and Agencies to eliminate unnecessary regulation and to promote increased understanding and ease of compliance by institutions that conduct federally supported or regulated research involving human subjects. Therefore, the Ad Hoc Committee developed a Model Federal Policy, which applies to

research involving human subjects that is conducted, supported or regulated by Federal Departments and Agencies. In accordance with the Commission's recommendation, the Model Federal Policy is based on Subpart A of the regulations of HHS for the protection of human research subjects (45 CFR Part 46). The Proposed Model Federal Policy developed by the Ad Hoc Committee was modified by OSTP to enhance uniformity of implementation among the affected Federal Departments and Agencies and to provide consistency with other related policies. The revised Model Federal Policy was concurred in by all affected Federal Departments and Agencies in March 1985.

An Interagency Human Subjects Coordinating Committee was chartered in October 1983 under the auspices of FCCSET to follow the Ad Hoc Committee. It is composed of representatives of all Federal Departments and Agencies that conduct, support or regulate research involving human subjects. The Committee is advisory to Department and Agency Heads and, among other responsibilities, will evaluate the implementation of the Model Federal Policy and recommend modification as necessary.

On June 3, 1986, OSTP published for public comment in the Federal Register (51 FR 20204) a Proposed Model Federal Policy for Protection of Human Subjects and Response to the First Biennial Report of the President's Commission. Over 200 written comments were received concerning the publication. The Interagency Human Subjects Coordinating Committee considered these comments in the revisions of the common Federal Policy which is proposed here for adoption by each of the Departments and Agencies listed. Response to the public comments and discussion of revisions made in the Proposed Model Federal Policy follow.

General Description of Responses

Two hundred and thirty four comments were received during the sixty day period following publication of the Proposed Model Federal Policy for Protection of Human Subjects [51 FR 20204]. Approximately 40 comments came in after the close of the public comment period. Of all the responses 192 came from medical schools and other academic institutions; 15 were from professional associations; 12 from Federal, state or county agencies, two from industry, and two from members of the public. Seventeen comments came from individuals who identified themselves as belonging to Institutional Review Boards (IRBs), and 36 were research administrators.

Almost unanimously, the respondents enthusiastically supported the concept of a Model Federal Policy. A few noted that the June 3 Federal Register publication of the Proposed Model Federal Policy did not address HHS intentions on retaining 45 CFR Part 46, Subpart B, concerning additional protections for prisoners as research subjects; Subpart C, concerning fetuses, pregnant women and human in vitro fertilization involved in research; and Subpart D, concerning children. HHS intends to retain Subparts B, C and D. The Notices of Proposed Rulemaking published here are the proposed replacement of the current Subpart A of the HHS policy. It should also be noted that the Department of Justice, Bureau of Prisons, intends to retain additional protections for prisoners codified at 28 CFR Part 512.

§_____.103 - Sixty Day Grace Period

The vast majority of the comments (223 of 234) addressed the "60 day grace period" which is included in HHS regulations at 45 CFR 46.103(f) but not in the Proposed Model Federal Policy. The grace period is the time interval between an institution's submission of a research grant application or contract proposal to HHS and certification of the institution's IRB

review and approval under current HHS regulations. Institutions that have Multiple Project Assurances on file with HHS have 60 days to finish IRB review and notify HHS. Two hundred and nineteen respondents disagreed with the deletion of the grace period from the Model Federal Policy and asked that the grace period be reinstated in the final Model Federal Policy. Summaries of their justifications are given below.

The arguments in favor of retaining the grace period are primarily based on the HHS time frame for preparation and review of research grant applications or contract proposals, the competitiveness of the review process and the quality of IRB review. For HHS-sponsored research there is usually about a nine month interval between the date an application is received and the earliest date an award can be made. For new applications, especially those which are submitted in response to a HHS Request for Applications, the time for preparation of the proposal is only 30 to 90 days. Some respondents indicated that this time frame is much different from the pace of biomedical science in which new publications, information or discoveries can make a methodology or approach obsolete within a few months. This discrepancy results in pressure upon principal investigators to revise and amend applications and proposals up until the last day before submission so as to have the best chance of success in the review process. Since an IRB cannot approve a tentative protocol, but must wait until the proposal is made final, requiring its review before the receipt date shortens an already brief preparation period and may adversely affect the quality of proposed research. Secondly, the requirement for prior IRB approval could adversely affect the quality of review. The IRB would have to be convened on short notice with possible reduced attendance by its members. This may well diminish the quality of review and create additional pressure on the IRB to approve proposals based upon limited information.

Arguments in favor of omitting the grace period are also based on quality of IRB review. These comments indicated that, if IRB review took place after a fundable priority score were obtained, the IRB might feel pressured to approve a questionable activity. In addition, the difficulties of tracking down an application which is moving through the review process to append an IRB certification of approval creates an administrative burden.

Response: The Interagency Human Subjects Coordinating Committee has revised §____.103(f) [§____.103(g) in the Proposed Model Federal Policy] to accommodate the concerns raised in the public comments. Under the revised section, the certification of IRB review and approval must accompany the application unless the Department or Agency specifies a later date for submission of the certification.

Although HHS intends to amend its current regulations to incorporate the language of the Model Federal Policy, it will retain a "grace period" for institutions that have multiple project assurances and announce the period through advisories, e.g. OPRR Reports or Public Health Service Guide to Grants and Contracts, which are routinely received by institutions. The "grace period" is the time between submission of an application for research support and submission of certification of IRB review and approval of the research proposed. Other Departments and Agencies will advise institutions of appropriate timing of certification through similar publications.

Other Comments and Revisions

While the Interagency Committee considered each comment carefully, the Committee made changes in the Proposed Model Federal Policy only when it decided that the suggestions would accomplish the following: strengthen the protections for human subjects; clarify the intention or requirements of the Model Federal Policy; or facilitate the administrative processes

required by the Model Federal Policy while maintaining or increasing human subjects protections. Areas in which there were a number of comments are highlighted below together with the rationale for the Interagency Committee's incorporating changes or retaining the provisions addressed in these comments.

§_____.101(b)(1) and §_____.101(b)(2)

Public Comments: One respondent suggested that no exemptions should be allowed if vulnerable subjects are involved. Concerning §____.101(b)(2), an exemption for certain types of research involving educational tests, survey procedures, interview procedures or observation of public behavior, one respondent noted that no mention is made of the potential impact that certain educational test surveys or interview procedures might have on children or adolescents and the Model Federal Policy should include consideration of this. To a few others, the rationale for the modifications was not clear. One response from an IRB recommended that no study involving educational tests where identifiers are recorded should be exempt from review and suggested that there are risks that are significant in addition to criminal or civil liability noted in this exemption when educational tests are used with identifiers. Another respondent thought that the Proposed Model Federal Policy language in the exemptions lessened human subjects protections. Similarly, another response suggested that the language be broadened to show that harming an individual's reputation in the community was a risk as well as financial standing and employability. Another comment indicated that if interviews yield identifiable data, regardless of the content, the research should be reviewed by an IRB.

Response: In response, the Interagency Human Subjects Coordinating Committee modified the language in §_____.101(b)(2)(ii) of the Model Federal Policy to include the reputation of an individual as a consideration in determining

whether research could be exempt. The Committee notes also that the Model Federal Policy exemptions at §_____.101(b)(1) and §_____.101(b)(2) will make less research exempt than now under 45 CFR 46.101(b)(3) and (b)(4).

§_____.101(b)(3)

Public Comment: §_____.101(b)(3) exempts certain research not covered under §_____.101(b)(2), involving use of educational tests, survey procedures, interview procedures or observation of public behavior. Several respondents believed the wording here was unexplained, unclear, and possibly weakened protections for human subjects from those afforded by 45 CFR 46.101(b). A few other respondents felt that further definitions would clarify the provisions. One response from an IRB indicated that few IRB members would be able to judge if this exemption applies in the absence of further legal guidance and that the exemption should be reconsidered.

Response: The Interagency Human Subjects Coordinating Committee notes that the exemptions at §_____.101(b)(2) and §_____.101(3) of the Model Federal Policy represent a consolidation of the exemptions at 45 CFR 46.101(b)(2),(3) and (4) of the current HHS regulations. The added portion at §_____.101(b)(3)(ii) of the Model Federal Policy indicates that some types of research involving the use of educational tests, survey procedures, interview procedures or observation of public behavior are exempt if a Federal statute requires without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter. The Department of Justice has indicated that 42 U.S.C. 3789(g) is such a statute. The Department of Education intends to take a departure from the Model Federal Policy at §_____.101(b)(3)(ii). The departure pertains only to research involving the use of educational tests, survey procedures,

interview procedures, or observation of public behavior, conducted under a program subject to the General Education Provisions Act and to the specific protections provided under that Act to participants in programs administered by the Department of Education.

§_____.101(b)(6)

Public Comment: The proposed §_____.101(b)(6) contains an exemption not found in 45 CFR Part 46 for taste testing. Seven respondents endorsed the new exemption, but one of these suggested the inclusion of testing involving already broadly marketed food containing approved types and levels of additives, unless quantities are limited. Another comment from an IRB suggested that the provisions on taste testing should require confidentiality.

Response: The Interagency Human Subjects Coordinating Committee modified exemption §_____.101(b)(6) to add that consumer acceptance studies are also included in the exemption. Also added to the exemption is a clarification that the food may contain an ingredient at or below the level and for a use found to be safe or an agricultural chemical or environmental contaminent at or below the level and for a use found to be safe by the FDA or approved by the Environmental Protection Agency (EPA) or the Food Safety and Inspection Service (FSIS) of the U.S. Department of Agriculture (USDA). This clarification is necessary because under the Food, Drug and Cosmetic Act, an approval of the use of a food additive sets forth not only the level at which the substance may be added, but also the technical effect for which it may be added (e.g., as a preservative) and the types of food to which it may be added (e.g., baked goods). Note that the exemption is not intended to apply to taste tests and quality evaluation studies if (1) a food ingredient

is being tested, and (2) the test substance is not on the FDA's Generally Recognized as Safe (GRAS) list; not a permitted food additive as tested; not normally found in food at the concentration being tested; is a pesticide; or contains a chemical residue for which the acceptable level has not been established by the FDA, the EPA and the FSIS of the USDA.

§_____.101(h)

Public Comment: This section concerns research in foreign countries. One respondent endorsed this provision; another suggested that the IRB, rather than Department or Agency Heads, should determine whether protections for subjects in foreign countries are at least equivalent to those provided in the Proposed Model Federal Policy.

Response: No change has been made in this Section. The Interagency Committee concludes that there is a need for oversight at the federal level concerning protections for subjects in foreign countries.

§_____.102

Twelve respondents addressed the distinction between "regulated research" and research that is "conducted or supported" by Federal Agencies or Departments. (See §_____.102 for a definition of regulated research.) Historically, one regulatory agency, the FDA, has relied on inspections of research projects to ensure compliance with Federal regulations regarding protection of human subjects. On the other hand, Departments and Agencies which sponsor research (e.g., HHS) have a system that requires that awardee institutions submit an assurance of compliance (assurance document) to the awarding Department or Agency which must be approved prior to the funding of research involving human subjects.

Of the 12 comments about this distinction, 11 argued against preserving the distinction. One respondent asserted that the continued distinction

could be maintained without creating any problems for an institution that is both supported and regulated. The other respondents felt that the continued distinction was contrary to the aims of uniformity and consistency of the Model Federal Policy, and that it created an unnecessary administrative burden on institutions that must comply with two sets of procedures. One respondent felt that the administrative distinctions were not burdensome and that the distinction could be maintained without problems for institutions at which both federally supported and regulated research are conducted.

Response: The Interagency Human Subjects Coordinating Committee considered these comments but determined that the Model Federal Policy should retain the distinction between "regulated research" and research that is "conducted or supported" by Federal Departments or Agencies. This distinction is necessary because "regulated research" is often privately financed by an array of sponsors ranging in size from multinational corporations to individual physicians and is conducted at a variety of locations ranging from large university hospitals to community hospitals to physicians' offices. The provisions for regulated research, therefore, must accommodate the diverse needs of those engaging in regulated research while also ensuring that human subjects are adequately protected. Requiring all sponsors to negotiate assurances would place a significant burden on many sponsors involved in regulated research, especially those engaged in research with a small number of patients in small institutions. For example, under the present regulatory structure, FDA will permit an investigational drug to be used by a physician on one patient for a treatment use under a treatment investigational new drug protocol or application (IND). For such a physician, the institution (if there is one), and the government, the assurance system would

require a significant expenditure of time with little gain. Under the existing system, which is not unduly burdensome, the physician must obtain IRB approval and informed consent before administering the investigational drug. Absent Federal support, however, he or she would not be required to negotiate the assurances set forth in §_____.103 of the Model Federal Policy. Eliminating the distinction between "regulated research" and federally conducted or supported research would mean that the physician would be compelled to learn about the assurance system and then negotiate and file an assurance, even if the investigational drug were to be given once to only one person. Consequently, the needs of small institutions and investigators are best met through the methods presently employed.

In addition, it should be noted that, contrary to the assertions made in several comments, the distinctions made for regulated research do not compel large institutions where research is regularly conducted to satisfy two different sets of regulations. A common set of provisions concerning IRBs and human subject protections apply to regulated research and to research conducted or supported by Federal Departments or Agencies, and this will continue to be the case.

Thus, the distinction for regulated research and federally supported or conducted research in the Model Federal Policy embodies the most effective and efficient manner for ensuring that regulated research is conducted in a manner that will assure the protection of human subjects.

§_____.102(g)

Public Comment: One respondent indicated that the term "IRB" should be defined.

Responses: A definition of IRB is now included in §_____.102(g): "IRB means an institutional review board established in accord with and for the purpose expressed in the Model Federal Policy."

§_____.103(a)

Several public comments indicated that this section is confusing with regard to (1) with whom an institution should file an assurance; (2) to whom an institution should report modifications or amendments to existing assurances; and (3) to whom an institution should report adverse effects or acts of noncompliance [particularly §_____.103(b)(3),(d),(e)]. Reporting some changes through OPRR was suggested as a possibility.

Response: The Interagency Human Subjects Coordinating Committee redrafted §_____.103 to place in a more prominent position the provision found in §_____.103(f) of the Proposed Model Federal Policy, which indicates that individual Department and Agency Heads shall accept the existence of a current assurance, appropriate for the research in question, on file with OPRR and approved for federalwide use by that office. When this type of assurance is used, all reports, except certification, required by the Model Federal Policy, must be submitted to OPRR as well as to the appropriate Department and Agency Heads.

In §_____.103(b)(3), an addition has been made to clarify that changes in IRB membership are reported by institutions to the appropriate Department or Agency head unless, in accord with §_____.103(a), the existence of an HHS approved assurance is accepted in lieu of submission of an assurance. In this case, changes in IRB membership are reported directly to OPRR.

§_____.103(b)(5)

Public Comment: Several comments addressed the requirements for §_____.103(b)(5), written procedures to ensure prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency Head of any unanticipated problems or scientific misconduct involving risks to human subjects or others; any allegation or finding of serious or continuing noncompliance with the Federal Model Policy or the requirement or determinations of the IRB; and any suspension or termination of IRB approval.

One IRB proposed language that would eliminate any implication that the IRB should necessarily be the body within an institution that is responsible for investigating and reporting noncompliance with human subjects regulations. More flexibility in administrative arrangements for reporting was urged. Other comments endorsed the proposed language of the Policy if there is recognition that most institutions must have their own due process and if some flexibility is permitted in reporting scientific misconduct. Several respondents noted that the terms "unanticipated problems," "scientific misconduct," and "risks to others" were unclear.

Several respondents also indicated that institutions should not report allegations of misconduct and noncompliance--only results of investigation or inquiry about such to Federal Department and Agency Heads. It was argued that some flexibility must be given to institutions, and that institutions should be allowed to screen out allegations that are frivolous, mischievous or lacking in substance. One respondent suggested that any additional policing actions are inappropriate and that only actions of institutions should be reported to Federal officials; otherwise, due process for researchers or other institutional personnel is jeopardized. Other reactions were that paperwork would increase if allegations are reported and that an

institution would be hesitant to use the suspension mechanism as a management tool if such a suspension must be reported to Federal offices because of infractions such as tardiness in responding to an IRB.

Response: The Interagency Committee clarifies that the word "others" in §_____.103(b)(5)(i) denotes other persons who are participating in clinical trials under the same or similar protocols or who may be affected by products or procedures that were developed on the basis of inappropriate or questionable research.

In addition, in §_____.103(b)(5)(ii) the Interagency Committee has modified the Model Federal Policy to delete the word "allegation." This Section now indicates that written procedures in assurances must ensure prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency Head of any instance of serious or continuing noncompliance with the Policy or the requirements or determinations of the IRB. While the Interagency Committee did not intend that institutions report frivolous situations, it does expect institutions to report serious instances of noncompliance in which there is some reasonable substantiation, even if a final institutional determination has not yet been made. In such cases, the Committee also expects prompt notification of the final decision by the institutions.

§_____.103(f)

Public Comment: Four respondents endorsed this section; one other noted that this provision was valuable to the IRB, and one suggested that it was a valuable provision in easing administrative burdens if the Office for Protection from Research Risks will accept minor rewording changes in current assurances on file to reflect changes in HHS regulations that result from adoption of the Model Federal Policy.

Response: §_____.103(f) in the Proposed Model Federal Policy has been moved to §_____.103(a). This section requires individual Department and Agency Heads, in lieu of requiring submission of a separate assurance, to accept the existence of a current assurance on file with the Office for Protection from Research Risks, HHS, which has been approved for federalwide use by that office. Also, this section has been modified slightly to indicate that not all types of assurances on file in OPRR are appropriate for federalwide use.

§_____.107(a) and (b)

Public Comment: §_____.107 addresses IRB membership. One response indicated that the membership requirements for IRBs have been changed in a way that decreases the protection to vulnerable groups in research projects.

Five commentators wrote with some concern about the language changes in this section from the language in the current HHS regulations, as follows. One response indicated distress over the language changes because the presence of an advocate for a vulnerable group as a voting member of the IRB has been of immense value, and strong language is urged to require members concerned with special populations. Several others commented that the Model Federal Policy language regarding representation of vulnerable subjects is weak compared to the HHS regulations, so that the welfare of vulnerable subjects may not be adequately represented. One response also reflected that it is "risky" to remove required representation for vulnerable subjects, and it should be mandatory that representatives of the subject population serve as full members of the IRB.

§_____.107(b), which addresses gender considerations in IRB selection, elicited a comment that the language eliminates bias or discrimination, but seven others indicated a negative response to the change from the current HHS regulations at 45 CFR 46.107(b) and urged retention of the requirement that no IRB may consist entirely of men or entirely of women. One respondent wrote that the new language is confusing, and that the term "nondiscriminatory effort" used in §_____.107(b) is unclear.

Response: The Interagency Committee expects that institutions will use good judgment and diligence in selecting persons as IRB members who can fulfill the requirements of §_____.107(a), so that persons of varying backgrounds will promote complete and adequate review of the research activities. In approving assurances, the Federal Departments and Agencies that conduct, support or regulate the research will review IRB composition to ensure that the membership is appropriate for the research, and may request that membership be supplemented if complete and adequate review of the research does not appear possible. Concerning gender representation of the IRB, the Interagency Committee notes that in seeking diverse membership on the IRB, the institution must consider both men and women who can contribute to the role of the IRB. Given the ready availability of well qualified persons of both genders, the Interagency Committee expects that only rarely, if ever, will an IRB consist solely of men or solely of women.

§_____.107(c) and (d)

Public Comment: §_____.107(c) and (d) require IRBs to include at least one scientific member, at least one nonscientific member and at

least one member unaffiliated with the institution. One comment was that changing the current 45 CFR 46.107(c) language to require one scientific member constitutes an improvement, but consideration should be given to smaller, particularly rural, institutions. Some allowance for review by a cooperating institution should be made, it was suggested.

Response: The Interagency Human Subjects Coordinating Committee notes that §_____.114 permits agreements between cooperating institutions under which the institution may, with the approval of the Department or Agency, use joint review, rely upon the review of another qualified IRB, or make other review arrangements aimed at avoiding a duplication of effort.

§_____.110

Public Comment: §_____.110 sets forth requirements for expedited review. Five respondents expressed concern that the conditions under which Department or Agency Heads may suspend, restrict or terminate approval of expedited review are not specified and that, consequently, each Head could have a separate agreement which might be burdensome for research institutions. One respondent suggested a clarification to indicate that a minor change in approved research could have an expedited review procedure only within the one year minimum annual review period of the IRB.

Response: The parenthetical clarification "(of one year or less)" has been added to §_____.110(a)(b)(2) to clarify the period for which IRB approval is authorized.

The Interagency Committee expects that Department and Agency Heads will base the authority to use expedited review on the "track record" of the institutions involved. For example, HHS generally permits institutions with Multiple Project Assurances to utilize the expedited review procedure. Other institutions may not use this type of review.

§_____.111

Public Comment: This section sets forth the criteria for IRB approval of research. A few commented on §_____.111(a)(3) concerning equitable selection of subjects, as follows: (1) institutions should be provided with a clear definition of "economically or educationally disadvantaged" persons; and (2) institutions need guidelines on involvement of these populations in research before they are included in the list of vulnerable populations. Another suggested that an additional safeguard would be that the IRB require an explanation by the investigator as to why research needs to be conducted involving a vulnerable population and that the IRB certify that such involvement is necessary. Another comment was that pregnant women should not necessarily be considered members of a vulnerable population.

Response: The Interagency Human Subjects Coordinating Committee made no changes in the Model Federal Policy at this time that specifically address these public comments but is concerned about adequate protections for vulnerable subjects and equitable selection of subjects and is continuing to study these issues. Sec.107(a) of the Model Federal Policy has been modified to strengthen consideration of interests of vulnerable subjects.

§____.114

Public Comment: §____.114 concerns cooperative research. Five responses raised the following points. The current provisions could result in many different requirements if each Department or Agency Head can make a determination about cooperative research projects. Similarly, one concern expressed was that the Model Federal Policy should permit cooperating institutions to decide among themselves how to enter into various alternatives named in the section, rather than require institutions first to obtain permission from the Department or Agency; to eliminate paperwork and time burdens does not further the protection of human subjects. The section appeared to another commentator as a hindrance to cooperative effort at the "grass roots" level where working together should be encouraged. Other suggestions were that the section should be expanded to include specific details for institutions, and that it should be made clear that the requirement for IRB review of cooperative research applies whether or not funds are involved.

Response: The Interagency Committee has formulated the Model Federal Policy in such a way that Department and Agency heads retain the authority to determine what levels and loci of review are appropriate, given the nature of the research to be conducted or supported and their judgment about the experience and expertise of the institutions to be involved in the collaborative research. In this way a balance between uniform review standards and flexibility can be maintained to protect human subjects of research.

§____.121

Public Comment: §____.121 is reserved. Some respondents questioned whether the provisions of Section 45 CFR 46.121 are still applicable since the comparable section in the Model Federal Policy is now reserved.

Response: The Interagency Human Subjects Coordinating Committee clarifies that the FDA requirements referenced in 45 CFR 46.121 (i.e., 21 USC 312, 355, 357, 812) still apply. However, the information called for by 45 CFR 46.121 was considered no longer necessary. This section has been designated as reserved in the Model Federal Policy so that the parallel numbering sequence between the HHS and FDA regulations for the protection of human subjects could be retained in the current Model Federal Policy.

§_____.124

Public Comment: §_____.124 states that Department and Agency Heads may impose additional conditions necessary for the protection of human subjects. One respondent expressed hope that the Department and Agency Heads would limit additional conditions to those required by statute.

Response: The Interagency Human Subjects Coordinating Committee agrees and indicates that it will work toward uniformity among Departments and Agencies.

Departures Proposed by Departments and Agencies

Public Comment: Several comments expressed concern that deviations from the Model Federal Policy could be abused, and departures should be limited only to those required by statute.

Concerning the VA departure, one comment stated that the Federal Departments and Agencies with which many universities are affiliated should be required to file assurances with OPRR when research administered by the affiliated institution is performed in a VA facility. Another urged that consent documents be as similar as possible among university hospitals, county hospitals and VA hospitals.

Response: The VA indicated that specification to the level of detail noted in the comments is beyond the level which is appropriate for a Model Federal Policy, and that cooperative arrangements are properly clarified by individual Departments and Agencies. VA elects to require that VA Medical Centers (VAMCs) which participate in cooperative or multi-hospital research projects obtain approval from their own IRBs for such research and does not contemplate approving §____.114 arrangements inconsistent with this policy. VA also elects not to require that VAMCs submit written institutional assurances under §____.103(a) to VA Central Offices. As the official responsible for the operation of VA research facilities, the Administrator will employ procedures other than the submission of written assurance from subordinate officials to assure compliance with VA policies.

On the issue of departure, the VA notes the statutory directive that it adopt the Model Federal Policy "to the maximum extent feasible consistent with other [statutory] provisions" which govern its conduct. 38 U.S.C. §4134. It has determined that adoption of the Model Federal Policy without departures is "feasible" and, thus, has withdrawn the departures noted in the June 3 Federal Register Notice. In notes, however, that certain provisions of the Model Federal Policy, particularly §____.101(b) and §____.116(c) and (d), will be narrowly construed in order to avoid inconsistency with other statutory directives.

FDA indicates that it has concurred in the Model Federal Policy. Since the Agency has already adopted regulations on informed consent (21 CFR Part 50) and on IRBs (21 CFR Part 56) elsewhere in Part ____ of this issue of the Federal Register, FDA is proposing to amend those regulations to eliminate certain inconsistencies with the Model Federal Policy. Nonetheless, because

of the statutory requirements described in the proposal (51 FR 20216), FDA's regulations will continue to depart from §_____.101(h) (requirements for foreign research) and §_____.116(d) (waiver of informed consent) of the Model Federal Policy.

The Department of Education proposes to make a departure from §_____.101(b)(3)(ii) of the Model Federal Policy that pertains only to research involving the use of educational tests, survey procedures, interview procedures, or observations of public behavior, conducted under a program subject to the General Education Provisions Act. Under this departure the exemption to the Model Federal Policy is revised to read as follows: "The research is conducted under a program subject to the protections of the General Education Provisions Act (GEPA), including GEPA Sections 400A (20 U.S.C. 1221-3), 438 (20 U.S.C. 1232g), and 439 (20 U.S.C. 1232h)."

The Department of Education proposes also to make a departure from §107(a) of the Model Federal Policy that pertains to membership of IRBs. This departure results from the special concern of the Department to provide additional safeguards in the Policy for mentally disabled persons and handicapped children who are subjects of research. Under this departure, the final sentences in §107(a) of the Policy are revised to read as follows: "When an IRB reviews research that deals with handicapped children or mentally disabled persons, the IRB shall include at least one person primarily concerned with the welfare of the research subjects. If an IRB regularly reviews research that involves other vulnerable categories of subjects, such as non-handicapped children, prisoners, or pregnant women, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects."

The HHS is withdrawing its departure from the proposed Model Federal Policy indicated in the June 3, 1986, Federal Register. This is a provision which is now found in the current HHS regulations at 45 CFR 46.101(i): "If, following review of proposed research activities that are exempt from these regulations under paragraph (b)(6), [of the current HHS regulations] the Secretary determines that a research or demonstration project presents a danger to the physical, mental, or emotional well-being of a participant or subject of the research or demonstration project, then federal funds may not be expended for such a project without the written informed consent of each participant or subject." While the Department has an obligation, pursuant to the conditions imposed upon its appropriations, to ensure that research activities do not present a danger to the physical, mental or emotional well-being of participants, as enacted by the most recent continuing appropriations act for HHS, this statutory requirement will be accomplished under §_____.101(d). This section indicates that Department or Agency heads may require that specific research activities or classes of research activities conducted, supported, or otherwise subject to regulation by the department or agency but not otherwise covered by this policy, comply with some or all of the requirements of this policy.

Lists of Subjects in the Notices of Proposed Rulemaking: Protection of human research subjects; Research conducted, supported, regulated; Institutional review boards; Informed consent; Cooperative research; Research investigators; Research institutions; Assurances of Compliance.

Enclosure E

I concur with proceeding to publish in the Federal Register as a proposed common rule the Federal Policy for the Protection of Human Subjects as transmitted by Dr. Graham in his letter of July 18, 1988.

APPROVED: /s/ William H. Webster DATE: 29 AUG 1988

Central Intelligence Agency
Washington, D.C. 20505

EXECUTIVE SECRETARIAT

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Remarks

STAT TO 6 & 17: [redacted] OMS, also received this 90-page package. Please coordinate with OGC regarding DCI's concurrence (see Enclosure E). If another appropriate official can concur, suggest

STAT this be done to meet deadline.

[redacted]
Executive Secretary

21 JUL 88
Date

3637 (10-81)

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

July 18, 1988

Dear Mr. Webster:

Enclosed for your clearance is the Federal Policy for the Protection of Human Subjects to be proposed for public comment in the Federal Register as a common rule (enclosure A). Adoption of this policy will implement a recommendation from the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research that "all federal departments and agencies adopt as a common core the regulations governing research with human subjects issued by the Department of Health and Human Services." This policy has been developed by the Interagency Human Subjects Coordinating Committee, a committee of the Federal Coordinating Council for Science, Engineering and Technology. The Interagency Coordinating Committee included a representative from your organization as well as eighteen other organizations (enclosure B).

Two organizations propose to depart from the Federal Policy, the Department of Education and the Food and Drug Administration (FDA). These departures and the FDA Notice of Proposed Rulemaking are included in enclosure C.

For your information, I am enclosing a common preamble (enclosure D) that will be published in the Federal Register and which provides some background to the proposed rule.

The Federal Policy has been in development for some time and has been widely shared in each of the organizations involved. Therefore, I am asking for clearance from all organizations within two weeks of the date of this letter so that we can proceed to publish in the Federal Register. OMB and the Office of the Federal Register have arranged for streamlined procedures for proposed common rule publication.

The Central Intelligence Agency (CIA) has indicated that it will follow the Federal Policy as adopted by HHS in its regulations, responding to Executive Order 12333 requiring the CIA to conform to guidelines issued by the Department of Health and Human Services.

L-266-15

(HHS). Although the CIA does not propose to codify the Federal Policy as regulations, I am asking for your concurrence prior to publication in the Federal Register.

Please return the signature page indicating your concurrence (enclosure E) to Dr. Joan P. Porter, Office for Protection from Research Risks, National Institutes of Health, Building 31, Room 4B09, 9000 Rockville Pike, Bethesda, Maryland 20892.

We want to move rapidly to ensure a coordinated federal approach for protection of human subjects in research. I believe promulgation of the common rule will help us achieve that goal. I appreciate your priority attention to clearance of these documents.

Sincerely,

William R. Graham

William R. Graham
Director

The Honorable William H. Webster
Director, Central Intelligence Agency
Washington, D.C. 20505

Enclosures

STAT cc: [redacted]
with enclosures